Remarks

In a response to a restriction requirement mailed to Applicants' Attorney on January 11, 2006. Applicants elected claims 1-3 and 12-13 (Group1) for further prosecution in this matter. As a result, claims 4-11 have been withdrawn and claims 1-3 and 12-13 remain pending. Applicants have furthermore amended claim 1 herein by incorporating the limitations of claim 2 therein which is hereby cancelled. Applicants have also elected the chemical species (1-H-Benzoimidazol-2-yl)(2,6-dichlorophenyl) methyl amine hydrochloride (the species of example 2) to serve as the starting point for Examiner Stocktons' search. The claims have been amended to this end and the arguments set forth below are tailored in this regard.

I. Rejection under 35 U.S.C. §112

The Examiner has rejected claim 3 under 35 U.S.C. §112(e) second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the present invention. It is further asserted that an "or" is needed before the last compound listed in the claims for the purpose of clarity. Claim 3 has now been amended in the manner. The rejection of claim 3 under 35 U.S.C. 102 (e) must therefore be withdrawn.

II. Double Patenting

The Examiner has provisionally rejected claims 1-3, 12 and 13 on the ground of non-statutory, obviousness-type double patenting as being unpatentable over claims 1-3, 8-15 and 16 of co-pending application U.S. Serial no. 10/771,185. It is further asserted that although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed invention is generally described in the co-pending, application. 10/771,185. This rejection is respectfully traversed for the following reasons.

Included herewith is a terminal disclaimer pursuant to form PCT/SB25 (09/06) that abbreviates the double patenting rejection over a pending reference application that is co-owned by the Assignee hereto. As such, the present application when issued as a patent will expire on the same date as that of co-pending U.S.S.N. 10/771,185, i.e., on or about February 3, 2024. In light of this submission, it is respectfully requested that the provisional double patenting rejection be withdrawn.

III. Rejection under U.S.C. 103(a)

The Examiner has rejected claims 1,3, 12 and 13 as being un-patentable for obviousness under 35 U.S.C. §103(a) over Japanese Patent No. 02-306916 to Nishi et. al. taken together with WO 2002/46169 to Hofmeister et. al. (or its English counterpart, U.S. Patent No. 6,686,384), either considering both alone or in combination. It is asserted that whereas the present application at issue discloses and claims benzoimidazole compounds, both Nishi et. al. 306,916 and Hofmeister et. al. '384 teach benzoimidazole compounds which are structurally similar to those claimed herein.

It is furthermore asserted by the Examiner in support of his rejection for obviousness that the difference between the compounds of Nishi et al. and the compounds instantly claimed is that the instant claimed compounds are generically described in Nishi et al. Secondly, it is also admitted that the difference between the compounds of Hofmeister et al. '384 and the compounds instantly claimed is that Hofmeister et al. discloses a secondary amine in versus a tertiary amine as instantly claimed {i.e., -NH- in Hofmeister et al. versus –NR5- wherein R5 is alkyl as instantly claimed}.

The Examiner then argues that in order to make a prima facie case of obviousness, it is sufficient that the prior art reference compound is so closely related to the claimed compound at issue that a chemist would find the difference an obvious innovation. It is further asserted that in the case here, each of Nishi et. al. and Hofmeister et al. '384 teach benzoimidazole compounds that are structurally similar to each other and to those of the present claimed invention and are therefore useful in treating some of the same diseases/disorders. Hence, the Examiner reasons the combination of Nishi et al. and Hofmeister et al. would also teach the instant claimed invention. The pharmaceutical compounds and compositions of the present invention would have been suggested by the references to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art. This rejection is also respectfully traversed for the following reasons.

The Examiner has respectfully erred in his determination that the compounds disclosed in Nishi et. al. and Hofmeister et.al. '384 are structurally similar to those claimed herein and therefore will be useful in the treatment of the same diseased states, thereby rendering

the present claimed invention obvious. For it is well established that structural similarity between chemical compounds alone is not sufficient to establish obviousness.

Chemical compounds present special issues of obviousness because of the limited number of elements, the existence of recurring groups or substitutes in complex molecules, the structural similarities within classes of related compounds, and the ability of chemists to undertake systematic experiments modifying known compounds. As a result, even if structural similarity may exist between the claimed and prior art subject matter, one must still show that the prior art suggests a reason or motivation to make the claimed compositions

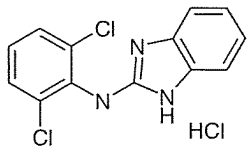
Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc. 471 F.3d 1369, 81 U.S.P.Q. 2d 1324 (Fed. Cir. 2006) citing In re May and Eddy 574 F.2d 1082, 197 U.S.P.Q. 601 (C.C.P.A. 1978)

Neither of the cited references, taken either alone or in combination, disclose or even suggest the claimed compounds of the present invention. Japanese Patent Application No. 02-306916 to Nishi et al. is directed to certain benzothiazoles and benzoimidazoles, which are disclosed as being useful as blood platelet adhesion inhibitors. Nishi et al. does not disclose any (benzoimidazol-2yl)-phenylamine compounds which are substituted in one or both of the ortho-positions of the phenyl ring as required in the claimed compounds of the present invention. For example, in the claimed compounds of the present invention substituents R6 and R7 cannot be hydrogen which is the case in the Nishi et. al reference.

Additionally, the claimed compounds of the present invention cannot be substituted in the meta- or para- position of the phenyl ring as disclosed by the compound in example 23 of Nishi et. al.. cited by the Examiner. Moreover, Nishi et al. does not suggest the use of the claimed compounds as NHE-3 inhibitors for the treatment or prophylaxis of a disorder of the respiratory system, a sleep-related respiratory disorders, sleep apneas or snoring. Therefore, the compounds of the present invention as claimed are not obvious in view of Nishi et al.

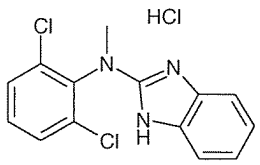
Hofmeister et al. '384 is directed to phenylamino-substituted benzimidazols wherein the amino-group can only be substituted with hydrogen in addition to the phenyl substituent R5 on the amino group. Were this to occur, a person skilled in the art would expect a lower solubility of these resulting compounds due to the additional lipophilic substituent. However, the compounds of formula I are as active as the compounds in Hofmeister et al. The following comparison experiment, shows that the solubility – in contrast to what a person skilled in the art would have expected – is higher for the compounds of formula I than for the compounds according to Hofmeister et al.:

Hofmeister et. al. '384 (WO 0246169)



IC50(NHE3) = 53 µm; solubility (6.25 µM; PBS buffer) see example 1 of WO 0246169. and U.S. Patent 6,686,384.

However, example 2 of the present application shows data for a compound as follows:



IC50(NHE-3) = 53 µm; solubility (150 µM; PBS buffer).

Hence the claimed compounds of the present invention are not obvious in view of Hofmeister et al.'384 due to the dramatic difference in solubility between the compounds. And even if one were to conclude the references were combine-able so as to support an

argument of obviousness. (for which it is submitted there is no motivation to do) the claimed compounds of the present invention with their exhibited surprising and unexpected properties would clearly not be reached and therefore cannot be regarded as obvious. For it is also well founded that in order to establish a prima facie case of obviousness under 35 U.S.C. §103 it is not sufficient to merely identify each element from the claimed invention in the prior art. A party alleging invalidity due to obviousness must articulate the reasons why one of oridinary skill in the art would have been motivated to select the references and combine them so as to arrive at the claimed invention at issue Abbott Laboraties v. Andrex Pharmaceuticals Inc. 452 F3d 1331, 1336; 69 U.S.P.Q. 2d 597 (Fed. Cir, 2006) sanofi-synthelabo Inc. v. Apotex Inc. 470 F3d 1368, 1379; 81 U.S.P.Q. 2d 1097 (Fed Cir. 2007) acting.

Here clearly, there is no such motivation Nishi et al disclose any (benzoimidazol-2yl)-phenylamine compounds which are substituted in one or both of the ortho-positions of the phenyl ring as required in the claimed compounds of the present invention. For example, with respect to the claimed compounds herein, substituents R6 and R7 cannot be hydrogen which **is** the case in the Nishi et. al reference. Therefore, this does not suggest or teach the benzamidazol phenylamine compounds with the substituted groups as disclosed herein nor does Hofmeister et al '384 provide any such teaching or motivation to do so since Hofmeister et al. '384 is directed to phenylamino-substituted benzimidazols wherein the amino-group can only be substituted with hydrogen in addition to the phenyl substituent R5 on the amino group. One cannot combine the teachings of Hofmeister with that of Nishi so as to come up with the claimed compounds of the present invention since they in fact teach away therefrom. Therefore, the rejection of claims 1,3,12 and 13 for obviousness under 35 U.S.C. 103 must respectfully be withdrawn.

In light of the foregoing amendments to the claims and arguments as to their patentability, it is respectfully asserted that the remaining pending claims recite patentable subject matter that is clearly distinguishable and an advance over the cited prior art. It is further respectfully requested that said rejections of the claims be withdrawn so that they might pass to allowance and issue. Should however, the Examiner still have some remaining issue(s) or concern(s), he is earnestly solicited to contact the undersigned

attorney so that the un-resolved matter might be overcome and resolved.

Respectfully submitted,

Craig M. Bell

Craig M. Bell
Registration No. 31,812
Attorney for Applicants

sanofi-aventis U.S. LLC
U.S. Patent Operations
Route #202-206 / P.O. Box 6800
MAIL STOP: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-2387
Telefax: 908-231-2626